REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at (858) 720-5133.

Status of the Claims

Pending claims

Claims 1 to 12, as filed, are pending.

Claims added in the instant amendment

In the present response, claims 13 to 20 are added. Thus, after entry of the instant amendment claims 1 to 20, will be pending and under consideration.

Outstanding Rejections

Claims 1 to 5 and 7 to 12 are rejected under 35 U.S.C. §112, second paragraph. Claims 1 to 12 are rejected under 35 U.S.C. §112, first paragraph, enablement requirement. Claims 1 to 12 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1 and 2 of USPN 6,692,742. Claims 1 to 12 are *provisionally* rejected under 35 U.S.C. §101, as allegedly claiming the same invention as that of claims 1 to 3 and 7 to 9, of co-pending USSN 10/098,874.

Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for Claim Amendments

Support for the new and amended claims can be found throughout the application for the skilled artisan. For example, support for claims directed to dosages of melphalan can be found, inter alia, on page 28, lines 15 to 28, of the specification; which corresponds to paragraph [0157] of U.S. Patent Application Publication serial no. 20040247621 ("the '621 publication"). Support for claims directed to various formulations of the pharmaceutical compositions of this invention can be

found, inter alia, on page 27, line 4, to page 30, lines 16; which corresponds to paragraphs [0152] to [0163] of the '621 publication.

Accordingly, Applicants submit that no new matter is introduced by the present amendments.

Species Restriction Requirement and Election

The Office alleged that the pending claims of the application are directed to several patentably distinct inventions under 35 U.S.C. §121, and Applicants were required to elect a single disclosed species. Applicants elected the species melphalan, where claims 1 and 7 are generic, and claims 5 and 11 specifically list several exemplary species, including melphalan.

Applicants thank the Examiner for noting that because the elected species is free of art, the search was expanded to other species.

Issues under 35 U.S.C. §112, second paragraph

Claims 1 to 12 are rejected under 35 U.S.C. §112, second paragraph, for reasons set forth in pages 2 to 3, of the OA. The instant amendment addresses these issues.

Issues under 35 U.S.C. §112, first paragraph

Enablement

Claims 1 to 12 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for the claimed invention, for reasons set forth on pages 3 to 7 of the OA.

The Office acknowledges that the specification is enabling for a combination of a reshaped PM-1 antibody and melphalan (see page 3, first sentence of this section, in the OA).

Deposit issues

To address the deposit issues for "PM-1" (see pages 4 to 5, of the OA), please note the amendment to claims 3 and 9, and the specification on page 9, lines 10 to 16, corresponding to paragraph [0065] of the '621 publication:

> [0065] ... the hybridoma cell line which produces PM-1 antibody has been internationally deposited under the provisions of the Budapest Treaty as PM-1 on Jul. 10, 1990 with the National Institute of

Bioscience and Human Technology, Agency of Industrial Science and Technology, of 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, as FERM BP-2998.

See also paragraphs [0204] to [0212] of the '621 publication.

This deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

Enablement issues

The Office alleges that the specification does not teach one of skill in the art to practice the full scope of the claimed invention without resorting to undue experimentation, i.e., the combination of a genus of nitrogen mustard anticancer agents and the genus of IL-6 receptor antibodies, as discussed on page 6, line 10, to page 7, of the OA. In brief, it is alleged that although the specification is enabling for practicing the species combination of the reshaped PM-1 antibody and melphalan, it would take undue experimentation to practice the full scope of the claimed invention, i.e., use of a combination of the genus of all anti-IL-6 receptor antibodies and the genus of all nitrogen mustard anticancer agents.

Antibody genus

The instant amendment addresses this issue; after entry of this amendment, the scope of the genus of anti-IL-6 receptor antibodies will be narrowed to encompass only anti-IL-6 receptor antibodies that inhibit signal transmission of IL-6 by blocking the binding of IL-6 ligand to IL-6 receptor (see section 1, "anti-IL-6 receptor antibody", pages 8 to 9 of the specification; or, paragraphs [0061] to [0065] of the '621 publication). Making and selecting for an antibody, such as a monoclonal antibody, that has such a focused activity is well within what the art considers routine screening, versus undue experimentation.

The specification details exemplary routine protocols to make antibodies that inhibit signal transmission of IL-6 by blocking the binding of IL-6 ligand to IL-6 receptor, see inter alia, section 2, "Antibody Produced by Hybridoma", pages 9 to 13 (paragraphs [0066] to [0085] of the '621 publication); section 3, "Recombinant Antibody", pages 13 to 15 (paragraphs [0086] to [0093] of the '621 publication); section 4, "Altered Antibody", pages 15 to 18 (paragraphs [0094] to [0105] of the '621 publication); section 5, "Antibody Fragments and Modified Antibody", page (paragraphs

[0094] to [0113] of the '621 publication); section 6, "Expression and Production of Recombinant Antibody, Altered Antibody, and Antibody Fragment" (paragraphs [0114] to [0132] of the '621 publication); section 7, "Separation and Purification of Antibody" (paragraphs [0133] to [0137] of the '621 publication); section 8, "Measurement of Antibody Concentration" (paragraphs [0138] to [0142] of the '621 publication); and, section 9, "Confirmation of the Activity of Antibody" (paragraphs [0143] to [0151] of the '621 publication).

Additionally, data validating that the PM-1 antibody – which is an antibody that inhibits signal transmission of IL-6 by blocking the binding of IL-6 ligand to IL-6 receptor – works synergistically with a nitrogen mustard anticancer agent to treat myeloma also validates the (as amended) claimed genus of antibodies that inhibits signal transmission of IL-6 by blocking the binding of IL-6 ligand to IL-6 receptor.

Accordingly, this specification teaches the skilled artisan how to make and use the (as amended) claimed genus of antibodies that inhibit signal transmission of IL-6 by blocking the binding of IL-6 ligand to IL-6 receptor to treat myeloma synergistically with a nitrogen mustard anticancer agent.

Nitrogen mustard anticancer agent genus

The Office alleged that although the specification is enabling for practicing the species combination of the reshaped PM-1 antibody and melphalan, it would take undue experimentation to practice the full scope of the claimed invention, including use of a genus comprising all nitrogen mustard anticancer agents. However, Applicants respectfully aver that because it is well accepted in this art that chemotherapeutic agents of the same class having similar structures (e.g., nitrogen mustard anticancer agents) have similar chemical properties, and thus exhibit similar pharmacological action through a similar mechanism. Nitrogen mustard anticancer agents are classified on the basis of their similar chemical structure. Therefore, the fact that melphalan – which is representative of known nitrogen mustard anticancer agents – provides a synergistic anti-myeloma therapeutic activity in combination with antibodies that inhibit signal transmission of IL-6 by blocking the binding of IL-6 ligand to IL-6 receptor, reasonably validates use of any nitrogen mustard anticancer agent in combination with an antibody that inhibits signal transmission of IL-6 by blocking the binding of IL-6 ligand to IL-6 receptor to act in synergy to treat myeloma.

The Office cites Moreau, et al. (2006) Blood 107:397-403, for the proposition that whether one anti-cancer agent would enhance other anti-cancer activities is unpredictable and would require actual experimentation, as explained in detail on page 6, lines 15 to 20, of the OA. However, the issue in this application is not whether one anti-cancer agent would enhance other anti-cancer activities. In contrast to Moreau, in the instant application the claimed genus at issue (nitrogen mustard anticancer agents) includes only compounds of the same class having similar structures and having similar chemical properties, and thus exhibit similar pharmacological action through a similar mechanism. The instant specification provides data affirming that a specie of the claimed genus of nitrogen mustard anticancer agents (melphalan) acts in synergy with an antibody that inhibits signal transmission of IL-6 by blocking the binding of IL-6 ligand to IL-6 receptor to treat myeloma. In particular, in the present invention the anti-cancer effect of the claimed combination of agents was effective in (exhibited) a dose-dependent manner.

The Office cites Dancey, et al. (2006) Nature Reviews 5:649-659, and in particular the paragraph bridging pages 649 to 650, for the proposition that "... no [synergistic] regimen is selected on the basis of foreknowledge of sensitivity of an individual patient's tumor to the drugs." (see page 6, line 21, to page 7, line 7, of the OA). However, a full reading of that section of Dancey, entitled "Why combine anticancer drugs" clarifies the cited passage as meaning "... no [synergistic] regimen is selected on the basis of foreknowledge of sensitivity of an individual patient's tumor to the drugs [as administered individually]." Dancey's theorem is that one skilled in the art cannot predict whether two drugs will act synergistically just on the basis of their individual clinical activities and characteristics, e.g., because they are "agents of known activity, with different mechanisms of resistance and minimally overlapping spectra of toxicity, at their optimal doses and according to schedules that are compatible with normal cell recovery", see, e.g., in the paragraph bridging pages 649 to 650 of Dancey:

> With few exceptions, curative drug treatments for cancer are due to combining agents of known activity, with different mechanisms of resistance and minimally overlapping spectra of toxicity, at their optimal doses and according to schedules that are compatible with normal cell recovery.

In contrast, as noted above, data as set forth in this specification verifies and enables the synergistic efficacy of the combination comprising a genus of nitrogen mustard anticancer agents (e.g., melphalan) with an antibody that inhibits signal transmission of IL-6 by blocking the binding

of IL-6 ligand to IL-6 receptor to treat myeloma. The concept of synergy of the claimed combination has been verified by experimental studies.

Nitrogen mustard anticancer agents are chemotherapeutic agents of the same class having similar structures having similar chemical properties, thus exhibiting similar pharmacological action through a similar mechanism. Thus, melphalan – which is representative of known nitrogen mustard anticancer agents – by providing a synergistic anti-myeloma therapeutic activity in combination with antibodies that inhibit signal transmission of IL-6 by blocking the binding of IL-6 ligand to IL-6 receptor, reasonably validates use of any nitrogen mustard anticancer agent in combination with an antibody that inhibits signal transmission of IL-6 by blocking the binding of IL-6 ligand to IL-6 receptor to act in synergy to treat myeloma.

Issues of nonstatutory obviousness-type double patenting

Claims 1 to 12 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1 and 2 of USPN 6,692,742, which read:

> 1. A method for treatment of myeloma which comprise administering a reshaped human PM-1 antibody with melphalan to a subject in need of such treatment.
> 2. The method of 1 wherein the reshaped human PM-1 antibody is the antibody hPM-1.

To address this issue a terminal disclaimer is attached herein.

Provisional rejection under 35 U.S.C. §101

Claims 1 to 12 are *provisionally* rejected under 35 U.S.C. §101, as allegedly claiming the same invention as that of claims 1 to 3 and 7 to 9, of co-pending USSN 10/098,874.

Applicants will hold this issue in abeyance until such time claims are held allowable.

CONCLUSION

In view of the foregoing amendment and remarks, and terminal disclaimer, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs, 35 U.S.C. §101 double patenting, and on the grounds of nonstatutory obviousness-type double patenting. In view of the above, claims in this application after entry of the instant amendment are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the unlikely event that the transmittal form is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing atty docket no. **350292000402**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 720-5133.

Dated: March 14, 2007

Respectfully submitted,

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